

Intravitreal Recombinant Tissue Plasminogen Activator Without Gas Injection in a Patient with Massive Submacular Hemorrhage Associated with Age-Related Macular Degeneration: A Case Report

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Abstract

Introduction: Submacular hemorrhage (SMH) is a leading cause of severe visual loss. Pneumatic displacement of SMH from the macular area using intravitreal injection of tissue plasminogen activator (tPA) and gas and vitrectomy with subretinal injection of tPA and intravitreal injection of gas have recently been used as the standard therapies for SMH patients. However, little has been reported on single intravitreal administration of tPA for SMH patients.

Case report: A 62-year-old male patient noted both blurred vision in his left eye and difficulty speaking (dysarthria) 1 day before admission. He was diagnosed with both massive SMH and cerebral infarction. Funduscopy revealed that the fovea was shifted to the inferonasal side due to a massive subretinal blood clot, and optical coherence tomography (OCT) revealed steep retinal detachment, hyper-reflective material representing a blood clot under the retina, and multiple large retinal pigment epithelial detachments (PEDs). The patient received a single intravitreal administration of tissue plasminogen activator. After vitreous injection, nearly all of the massive subretinal blood clot moved to the peripheral retina, and the fovea returned to the appropriate position. His best corrected visual acuity improved from 20/250 to 20/100.

Conclusion: The present study showed a favorable outcome of a patient with a massive SMH complicated by cerebral infarction after receiving a single intravitreal administration of tPA. We hope that the single intravitreal administration of tPA can be applied for SMH patients who are not appropriate for surgery.

Keywords: Submacular hemorrhage; Intravitreal injection of tissue plasminogen activator; Age-related macular degeneration; Cerebral infarction

Abbreviations

SMH: Sub Macular Hemorrhage; tPA: tissue Plasminogen Activator; OCT: Optical Coherence Tomography; PED: Pigment Epithelial Detachment; anti-VEGF: anti-Vascular Endothelial Growth Factor, AMD: Age-Related Macular Degeneration

Introduction

Submacular hemorrhage (SMH) is defined as a blood clot between the neural retina and the retinal pigment epithelium and is a leading cause of severe vision loss. Several factors, such as limited transportation of nutrients from the choroid [1], traction of the retina [2], and release of toxic substances (fibrin [3], iron [4], and hemosiderin [5]) from a submacular blood clot have been considered to induce damage to the photoreceptor cells and retinal pigment epithelium. Surgical removal of the submacular blood clot was introduced more than two decades ago, and remarkable progress has been made with regard to the surgical technique and outcome. Pneumatic displacement of the SMH from the macular area using intravitreal injection of tissue plasminogen activator (tPA) and gas [6] and vitrectomy with subretinal injection of tPA and intravitreal

injection of gas [7] have been recently used as the standard therapies for SMH patients.

Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs is the standard therapy for age-related macular degeneration (AMD) patients, and the risk of complication after vitreous injection is very low [8]. Nevertheless little has been reported on the single intravitreal administration of tPA for SMH patients.

We report a case of a 62-year-old male with both massive SMH and cerebral infarction and describe his progress after a single intravitreal administration of tPA.

Case Report

A 62-year-old male patient who had right hemiplegia was admitted to our department for treatment of a massive SMH in his left eye. He had a cerebral infarction episode with otherwise unremarkable ocular history. He noted both blurred vision in his left eye and difficulty speaking (dysarthria) 1 day before admission. His best corrected visual acuity was 20/250. Funduscopy revealed a massive subretinal blood clot at the posterior pole, a shift of the fovea to the inferonasal side, and multiple large pigment epithelial detachments (PEDs) including at the posterior pole (Figure 1).

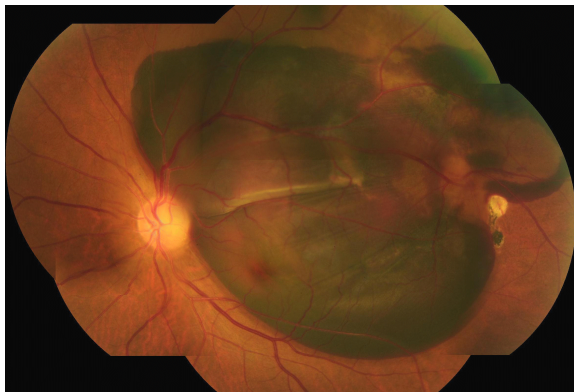


Figure 1: Fundus photograph of the patient before injection. Fundus photograph from his first visit. A subretinal blood clot and multiple large pigment epithelial detachments were observed. The fovea was shifted to the inferonasal side due to a subretinal hemorrhage.

Optical coherence tomography (OCT) was performed, which confirmed steep retinal detachment, hyper-reflective material representing a blood clot under the retina, and multiple large PEDs (Figure 2A-D).

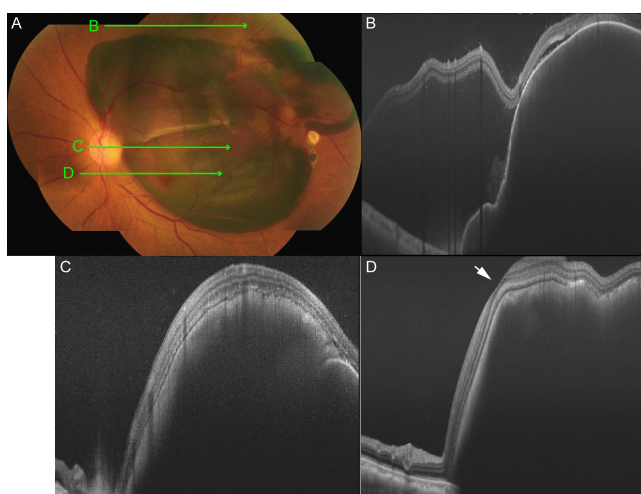


Figure 2: OCT of the patient before injection. A: Fundus photograph (Figure 1). B: Large PEDs and subretinal fluid were observed. C: Subretinal hemorrhage and large PEDs were observed. D: Subretinal hemorrhage was observed. The white arrow shows the fovea.

The examination of the fellow eye was unremarkable. After a discussion with the patient about surgery, including about keeping a prone position postoperatively, a single intravitreal administration of 20 µg of tPA (monteplase; Eisai) was undertaken. Three days after the injection, almost all of the massive subretinal blood clot had moved to the peripheral retina, and the fovea returned to the appropriate position (Figure 3).

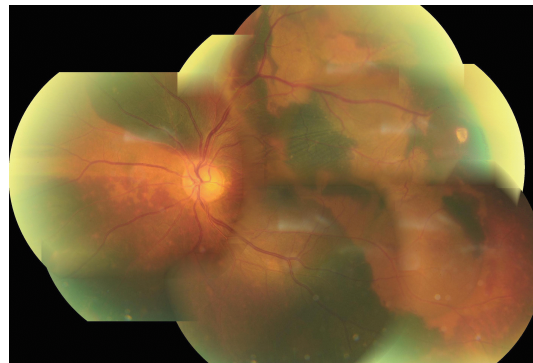


Figure 3: Fundus photograph of the patient after injection. Fundus photograph of three days after the injection. A subretinal blood clot moved to the peripheral retina, and the fovea returned to the appropriate position.

His best corrected visual acuity increased to 20/100. OCT showed multiple large PEDs and subretinal fluid with a residual blood clot (Figure 4A-D). We diagnosed SMH secondary to polypoidal choroidal vasculopathy based on the multiple PEDs; however, the patient did not undergo anti-VEGF therapy due to a new-onset cerebral infarction (dysarthria).

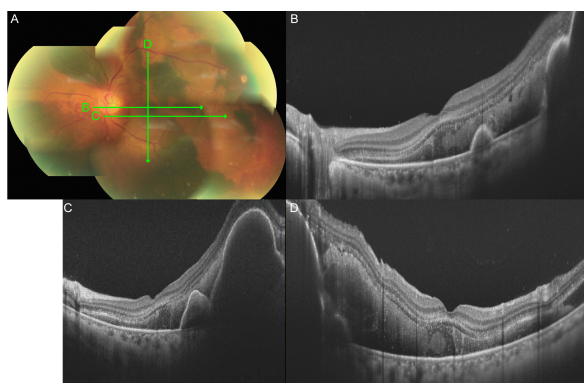


Figure 4: OCT of the patient after injection A: Fundus photograph (Figure 3). B-D: Multiple PEDs and subretinal fluid with a residual blood clot were observed.

Discussion

The present study showed a favorable outcome of a single intravitreal administration of tPA for a patient with a massive SMH complicated by cerebral infarction. The submacular blood clot was successfully displaced from the macular area, and the VA significantly improved after injection without limiting the postoperative patient posture.

SMH, arising from AMD and a retinal macroaneurysm, is a leading cause of severe visual loss according to natural history studies [9]. Surgical removal of the submacular blood clot was reported in the 1980s [10]; however, the results showed no clear benefit from invasive surgery, severe postoperative complications, and extraction of the RPE

with the blood clot [11]. To perform a minimally invasive surgery, tPA was introduced to dissolve and remove the blood clot through a small retinotomy site [12]. The use of tPA in the management of SMH showed significant vision improvement and has become widely accepted. The present surgical strategy [13,14] involved pneumatic displacement of the SMH from the macular area using tPA and gas injection. These surgical treatments require the patients keep a prone position for at least 1 day postoperatively and include the risk of reoperation. Patients with AMD, a major cause of SMH, often have a history of oral anticoagulants and cerebral infarction, and there has been a case in which the condition of patients prevented performing vitreous surgery because they could not maintain a prone position due to hemiplegia or dementia. In this case, the patient needed some assistance when changing position, sitting up in bed, and moving from bed to chair due to right hemiplegia, therefore he declined the surgery which requires keeping a prone position postoperatively.

The introduction of anti-VEGF treatment resulted in significant improvement of vision in AMD patients, and numerous vitreous injections have been performed. It is well accepted that the risk of complications after vitreous injection is very low [8]; however, there have been a few reports concerning single intravitreal administration of tPA for SMH patients. Tsymanava reported a comparative study of intravitreal tPA with and without gas injection for SMH [15], and although single intravitreal tPA injection did not represent an ideal result, the former resulted in an increase of 0.4 logMAR, and the latter resulted in a decrease of 0.1 logMAR. Therefore, this group advocated intravitreal tPA with gas injection over single intravitreal tPA injection. In our case, the fovea was shifted to the inferonasal side due to a massive SMH, and a large PED was located near the macular area. A previous report noted that massive SMH is difficult to displace using the aforementioned surgical strategy [16] and advised against subretinal tPA injection for a SMH patient with pre-existing PED due to tears in the RPE [17]. Additionally, this patient had difficulty in maintaining a prone position due to concomitant cerebral infarction. The aim of therapy for SMH is to displace the blood clot from the macular area and is based on two mechanisms: the effect of gas inducing a rolling action on the hemorrhage [6] and the effect of gravity working upon the hemorrhage [18]. The report concerning the effect of gravity showed that a large subretinal hemorrhage treated with single tPA injection migrated inferiorly in a gravity-dependent fashion and that a small subretinal hemorrhage treated with single tPA injection showed no subretinal migration. The present study showed displacement of a massive blood clot from the macular area by single intravitreal administration of tPA without the limitation of postoperative patient posture, suggesting that the massive submacular hemorrhage is likely to migrate inferiorly from the macular area by a single intravitreal administration of tPA. There is no doubt that administration of tPA and gas is the clinical gold standard; however, we believe that single intravitreal administration of tPA is helpful for SMH patients with complications, such as cerebral infarction. Furthermore, this method would be cost-effective and useful for medical care located in a remote area.

Diffusion of tPA through the retina is a controversial issue. The pore size of the outer limiting membrane is approximately 30 Å, corresponding to molecules of 50 kDa, and the tPA molecule is 70 kDa; therefore, tPA does not theoretically diffuse across the retina. Kamei et al. demonstrated the injection of tPA into the vitreous of rabbits with intact or subretinal hemorrhages and showed that the tPA signal failed to pass through the intact retina and that the tPA signal diffused across the retina, respectively [19]. They hypothesized that

tPA could diffuse across the retina due to microscopic retinal tears that occurred secondary to the subretinal hemorrhage, and our result support this hypothesis.

Conclusion

The present study showed a favorable outcome of a single intravitreal administration of tPA for a patient with a massive SMH complicated by cerebral infarction. We hope that the single intravitreal administration of tPA can be applied for SRH patients with complications.

Consent

The injection of tPA for this patient was approved by the ethics committee of Kawasaki Medical School (2014-8). Written informed consent for the injection of tPA and publication of this case report was obtained from the patient.

Competing Interest

The authors declare that they have no competing interests.

Author's Contribution

H.K. participated in the design of the study and wrote the manuscript. M.N. and N.O. treated the patient. J.K. reviewed the manuscript. All authors read and approved the final manuscript.

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